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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,299	10/16/2003	John Finn	020801-000320US	2636

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EXAMINER	
GUIDRY, GUY L	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/688,299	FINN ET AL.	
	Examiner	Art Unit	
	Guy Guidry, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-25* is/are pending in the application.

4a) Of the above claim(s) *26-39* is/are withdrawn from consideration.

5)☒ Claim(s) *40* is/are allowed.

6)☒ Claim(s) *1-8, 10-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a response filed 29 August 2006 to the Office Action mailed 7 March 2006. Claim 9 is canceled. Claims 26-39 are withdrawn. Claims 1, 5-6, 10-12 and 14 have been amended. Claims 1-8, 10-40 are currently pending in this application. Claims 1-8, 10-25 are under consideration in this Action. All previous objections/rejections not repeated herein are hereby withdrawn. Previous rejections to canceled claims have been rendered moot by Applicant's cancellation of those claims. A response to Applicant's arguments will be set forth, where appropriate, immediately following any statement of rejection repeated herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 10-25 stand rejected under 35 USC 112, 1st paragraph, as failing to comply with the written description requirement.

The rejection is of record. Applicant argues that that the claimed expression cassettes are sufficiently described in the specification. Applicant further argues that the specification describes numerous secretable domain sequences and that the specification describes two representative species of the claimed genus of said cassettes and thus the Applicants and possession of claimed genus of expression cassettes.

Response to arguments

Applicant's arguments have been considered and they are not persuasive. The crux of the written description rejection was not that HIV-TAT does not translocate across plasmalemma of many types of cells but that the claims are directed to any secretion domain that is fused to an RNA polymerase(s) (RNAPs) which must have the prescribed function of facilitating membrane translocation while concomitantly not hindering RNAP function. Thus, the claims are directed to a genus in terms of a fusion structure containing a domain allowing for membrane translocation while preserving RNAP function.

Given the number of potential secretion domains that can be fused with various RNAPs, the number of potential RNAP-secretion domain fusion protein combinations would be large. As was noted in the previous Action, the specification discusses secretion domains (signal peptides and protein transduction domains, specification pp. 23-24) polypeptide sequences which when linked to another polypeptide are given to create fusion proteins that are able to enter cells upon cell contact. However, the only relevant examples of secretion domain-RNAP fusion proteins are limited to two specific embodiments of which are SEQ ID NOs: 1 and 21, fused to a T7 RNA polymerase and used to transfect Neuro 2A cells and BHK cells respectively (specification pp. 50-54 1, Examples 2-3). Given that the various secretion domains vary in size from tens to hundreds of amino acids, one could not envisage which structures would encode secretion domain-RNAP fusion proteins where the size of the secretion domain would not confer steric interference of polymerase activity. With respect to the particular

secretion domain disclosed (i.e. claim 8, SEQ ID NO: 19 encoding an IL-2 secretion domain), one of skill would not be able to envisage the broad genus of any RNAP, with which the IL-2 secretion domain fusion would function in both translocation across any cellular membrane while preserving polymerase activity.

Given the large breadth of the fusion secretion domain-RNAPS embraced by the rejected claims, and given the limited description from the instant specification of such fusion proteins, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to describe the broadly claimed genus of secretion domain-RNAP fusion proteins. Moreover, an applicant claiming a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from other species. Therefore, the skilled artisan would reasonably have concluded that Applicants were not in possession of the claimed invention.

Claims 1-8, 10-25 stand rejected under 35 U.S.C. 112, 1st paragraph, as failing to comply with the enablement requirement.

The rejection is of record. Applicant argues that claim 10 has been amended to reflect that the claimed nucleic acids find use both in vivo and in vitro. Applicant further argues that the claimed composition required only one enabled use for patentability. Applicant argues that the teachings of the specification and the state of the art at the time of filing of the present invention, the skilled artisan would recognize that expression of the claimed cassette in to mammalian cell types in vitro would lead to the correlation

that the claimed nucleic have use expression of a product of interest in mammalian cell in vivo.

Response to arguments and amendments

Applicant's arguments have been considered and they are not fully persuasive. While enabling for expression vector compositions comprising two fusion RNA polymerases (RNAP), specifically VP22-T7-RNAP and TAT-T7-RNAP, the specification does not enable a person of skill in the art to which it pertains to make and use the broad genus of any secretion domain-RNAP commensurate in scope with the claims. In addition, the claims read on gene therapy, insofar as being directed to a vector containing a secretion domain-RNAP fusion protein in a vector to encode a therapeutic product of interest. Applicant is directed to the previous rejection under 112 § first paragraph which in incorporated herein.

Breadth of the claims/ nature of the invention

The claims are broad in scope in that base claim 1 is directed to vast combination of secretion domain-RNAP fusion proteins, as discussed above. Specifically, the claims are directed to a genus of secretion domains that is fused to a genus of RNA polymerases (RNAPs) which must have the prescribed function of facilitating membrane translocation while concomitantly not hindering RNAP function. Thus, the claims are directed to a genus in terms of a fusion structure containing a domain allowing for membrane translocation while preserving RNAP function; consequently, the number of potential RNAP-secretion domain fusion protein combinations would be substantial. Structural comparisons between known protein

secretion domains are not always informative with respect the mechanism of transduction (see Schwarze et al., *supra*, Trends Pharmacol. Sci., 2000, 2 l:45-8; p. 45, col. 3). Given that the various secretion domains vary both in size and presumptive method of membrane translocation, the specification is not enabling for construction of a genus of structures which would encode secretion domain-RNAP fusion proteins where the size of the secretion domain would not confer steric or functional interference of polymerase activity. Therefore, the disclosure is not enabling for a genus of structures (secretion domain-RNAPs) which the claims encompass. In addition, the claims are broad in being directed to membrane transduction (i.e. cell transfection) of any cell in any organism. As noted previously, the invention is directed to expression of therapeutic products in claims 9 and 10, which necessarily reads on *in vivo* application and in the context of the instant claims would read on gene therapy.

State of the art/unpredictability of the art

As indicated above, one of skill would not be able to envisage all the structures encompassed by the claims, given the prescribed functionality, thus there would be a large degree of unpredictability in regard to the various secretion domain-RNAP fusion proteins. Specifically, it would be unpredictable whether the secretion domain-RNAP fusion would both traverse any cell membrane and subsequently whether the RNAP would function in catalyzing transcription. Therefore, in determining the identity of various fusion constructs that would encode secretion competent RNAPs, one of skill would have to be apprised of the particular mechanisms by which the secretion domains facilitate membrane transduction. For example, HIV TAT domain would not form a

secretable RNAP for a genus of membranes because TAT requires cell surface heparan sulfate proteoglycans to facilitate membrane transduction (see especially the Abstract of Rusnati et al., 1997, J. Biol. Chem., 272(17): 11313-11320 and the Abstract and pages 3256-7 of Tyagi et al., 2001, J. Biol. Chem., 276(5):3254-61). Therefore in determining the identity of various fusion constructs that would encode secretion competent RNAPs, one of skill would have to be apprised of the particular mechanisms by which the secretion domains facilitate membrane transduction. As previously noted, with respect to the particular secretion domain disclosed (i.e. claim 8, SEQ ID NO:19 encoding an IL-2 secretion domain), one of skill would not be able to envisage the broad genus of any RNAP, with which the IL-2 secretion domain fusion would function in both translocation across any cellular membrane while preserving polymerase activity.

Additionally, while the level of skill of an ordinary person in the art is high, with respect to claims 9 and 10 and gene therapy, the art is highly unpredictable. For example, vectors used to deliver constructs encoding therapeutic products may be erroneously inserted into a particular gene resulting in unknown, adverse or detrimental effects (see especially Juengst, 2003, BMJ, 326: 1410-1411, discussing that gene transfer often has multiple unpredictable effects on cells). Additional obstacles to successful practice of the invention include poor efficiency of delivery of the gene to the targeted cells, poor transformation efficiency of target cells, and unpredictable and transient expression of the transgene in target cells (see especially Verma et al., Nature, 1997, 389: 239-242). Furthermore, the fusion proteins could elicit immune toxicity in the subject being treated. Assuming successful transcription, a gene of

interest encoding a therapeutic product would not necessarily be translated at all, since the transcription is cytoplasmic and the mRNA not capped, the product could be degraded or be too unstable to undergo translation.

Amount of direction or guidance

There is general guidance provided to a number of types of RNA polymerases, spanning a genus that includes both phagemid/viral RNAPs to eukaryotic RNAP that could potentially function as RNAP fusions. A broad variety of membrane secretion domains, signal peptides and protein transduction domains that could presumably be employed to generate a secretable RNAP are discussed in general terms. The only specific guidance is limited to two T7-RNAps discussed above. Also, there is general guidance provided as to the identity of some therapeutic products of interests (specification pp. 33-36) with respect to gene therapy. However, the only relevant guidance as to gene therapy or treatment of disease is prophetic in nature (e.g. single chain insulin on pp. 34-38 and suicide gene/prodrug systems pp 35-36 of the specification). Otherwise, there is no substantial relevant guidance provided as to using the claimed invention *in vivo*.

Number of working examples/level of skill/ quantity of experimentation necessary to make or use the invention.

As noted above, two working examples of secretion domain-RNAP are provided although no working example of the RNAP fusion protein recited specifically in claim 8, an expression vector with an IL-2 secretion domain-RNAP fusion construct, is noted in the specification. With respect to *in vivo* embodiments of the inventions directed in

claims 9-10 and gene therapy, two examples of transfection are provided but are limited to an *in vitro* context; no relevant *in vivo* examples provided. Also, the level of skill in the art required to practice the claimed invention is high. However, given the unsolved hurdles to successful practicing of the invention, the level of unpredictability in the art and lack of relevant working examples, it must be considered that the skilled artisan would be required to conduct experimentation of an undue nature in order to attempt to practice the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 9-25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Dalby et al. (US Pat. 6,773,920) in view of Deng and Wolff (Gene, 1994, 143: 245-249) as evidenced by Mizuguchi et al., (Mol Ther. 2000 Apr;1(4):376-82).

This rejection is of record. Applicant argues that the combination of references fails to teach all of the claimed limitations. Applicant argues that the instant claims are directed to an expression cassette comprising:(a) a eukaryotic promoter and a first RNA polymerase promoter operably linked to a nucleic acid encoding a secretable RNA

polymerase (sRNAP), and a first internal ribosome entry site (IRES); and (b) a second RNA polymerase promoter operably linked to a nucleic acid encoding a product of interest and a second IRES. Applicant alleges that Dalby et al. fails to teach or suggest an expression cassette comprising a first RNA polymerase promoter operably linked to a nucleic acid encoding a sRNAP and a second RNA polymerase promoter operably linked to a nucleic acid encoding a product of interest.

Applicant further argues that Deng et al. and Mizuguchi et al. do not supply the teaching that is allegedly lacking in Dalby et al. Applicant argues that Deng et al. teaches an autogene plasmid with a first T7 promoter operably linked to a T7 RNA polymerase and encephalomyocarditis (EMC) untranslated sequence (see, e.g., Figure 1A), but fails to teach or suggest an expression cassette comprising a second RNA polymerase promoter operably linked to a nucleic acid encoding a product. Applicant argues that Mizuguchi et al. teaches a bicistronic vector with Beta-actin promoter operably linked to a first gene and an IRES-dependent second gene (see, e.g., Figure 1), but fails to teach or suggest an expression cassette comprising a first RNA polymerase promoter operably linked to a nucleic acid encoding a sRNAP and a second RNA polymerase promoter operably linked to a nucleic acid encoding a product of interest, as required by the present claims.

Response to arguments and amendments

Applicant's arguments have been considered and they are not persuasive. Applicant mischaracterizes the *combined* teachings of Dalby, Deng, Mizuguchi, which considered together, meet the limitations of the instant rejected claims.

Specifically, Dalby et al. teach compositions where a cell-modifying polypeptide linked to a secretion domain such as T7 RNAP-VP22 may direct T7 promoted gene expression of a nucleic acid composition comprising a T7 promoter and a sequence encoding a product of interest (col. 9, lines 47-53). Dalby et al. also teach such a vector construct with a nuclear promoter (see the P_{CMV} in figs. 5 and 6). Thus, Dalby teaches an expression cassette comprising a first RNA polymerase promoter operably linked to a nucleic acid encoding a RNAP and a second RNA polymerase promoter operably linked to a nucleic acid encoding a product of interest. While Dalby et al. teach a method for modulating expression of a target gene by contacting a cell with a regulatory agent-translocating peptide fusion wherein the regulatory agent modulates expression of a target gene (Col. 44, claim 5), Dalby et al. do not specifically teach the use of internal ribosome entry sites (IRES).

Deng et al. teach an autogene vector containing a T7 promoter, encephalomyocarditis (EMC) internal ribosome entry sequence (IRES), and T7 RNA polymerase and transfection and self-amplification wherein the RNA polymerase is shown to enter the cell cytoplasm and carry out template-dependent synthesis of RNA in 3T3 fibroblasts (see especially the Abstract, the Introduction, p. 245, col. 2 to p. 246). Mizuguchi et al., teach a vector with nuclear promoter and first gene upstream of an IRES-dependent second gene in a bicistronic expression vector (see especially p. 378, fig 1). Mizuguchi et al. disclose vectors comprising for example, (in linear order) Beta actin promoter (first RNA polymerase promoter), luciferase, an IRES, Kozak sequence second gene of interest (p. 377, col. 1, ¶1). As would be recognized by a person of

ordinary skill in the art, the Kozak sequence is engineered into the vector to promote the action of RNA polymerase, thus meeting the instant limitations of first and second RNA polymerase promoters operably linked to secretable RNA polymerase and a second product of interest.

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made, in creating an expression vector for a secretable RNA polymerase, to design the vector so that to high levels of heterologous protein would be expressed. A person of skill would choose a design in which high levels of transcripts possible via an autogene configuration in the manner of Deng et al. and enhanced translation in the absence of mRNA capping through the use of IRESs and promoted by a Kozak sequences as taught by Deng et al. and Mizuguchi et al, particularly if the vector could be generated by splicing the relatively small coding sequence for a T7 RNAP and IRES in the manner of Deng et al. and Mizuguchi et al., into a preexisting vector of the type described by Dalby et al. Absent evidence to the contrary, the skilled artisan would have a reasonable expectation of success in combining these teachings to generate a vector with a two RNA polymerase promoters, self amplifying secretable polymerase and IRES sequences to facilitate translation of uncapped cytosolic message for heterologous proteins as embraced by the inventions of the instant application.

Conclusion

Claim 40 is allowed.

Claims 1-8, 10-25 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Guy Guidry, Ph.D. whose telephone number is 571-272-7928. The examiner can normally be reached on Monday through Friday 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Guy Guidry, Ph.D.

Examiner

Art Unit 1636

DANIEL M. SULLIVAN
PATENT EXAMINER